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(71) Applicant (for all designated States except US): **THE BRIGHAM AND WOMEN'S HOSPITAL, INC.** [Stateless/US]; 75 Francis Street, Boston, MA 02115 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **JIANG, Yandong** [CN/US]; 42 Park Street, North Reading, MA 01864 (US). **FERRIGNO, Massimo** [US/US]; 45 Longwood Avenue, Apt. C, Brookline, MA 02446 (US).

(74) Agent: **SAMPLES, Kenneth. H.**; Fitch, Even, Tabin & Flannery, Suite 1600, 120 South LaSalle Street, Chicago, IL 60603 (US).

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(54) Title: METHOD FOR DECREASING BODY TEMPERATURE BASED UPON LATENT HEAT OF FUSION

(57) Abstract: The present invention is concerned with rapidly lowering the body temperature of a patient by having them inhale frozen particles. These particles melt in the patient's respiratory tract and are expelled as liquid droplets when the patient exhales. The invention includes not only the method for reducing body temperature, but the mists that are used in this method as well.

Method for Decreasing Body Temperature Based Upon Latent Heat of Fusion

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Cross Reference to Related Applications

The present application claims the benefit of U.S. provisional application no. 60/572,470 filed on May 20, 2004, which is incorporated in its entirety herein by reference.

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Field of the Invention

The present invention is directed to methods for rapidly decreasing the body temperature of a patient. These methods involve having the patient inhale a mist containing small-diameter ice particles. The particles enter a patient's respiratory tract where they are converted into liquid droplets and then exhaled. The conversion from solid particle to liquid droplet is accompanied by heat exchange resulting ultimately in a decrease in the patient's body temperature.

Background of the Invention

Hypothermia may be induced by physicians to protect tissue during cardiac surgery or surgery on cerebral vessels (Silverberg, *et al.*, *J. Neurosurg.* 55:337-346 (1981)). It has also been used to protect brain tissue following severe traumatic injury (Marion, *et al.*, *N. Eng. J. Med.* 336:540-546 (1997)) and during resuscitation from cardiac arrest (*N. Engl. J. Med.* 346:549-556 (2002)). In addition, it has been suggested that rapidly reducing body temperature may be beneficial to stroke patients (Schwab, *et al.*, *Stroke* 29:2461-2466 (1998)) and in the treatment of hemorrhagic shock (Kim, *et al.*, *J. Trauma: Injury Inf. Crit. Care* 42:213-222 (1997)); Kim, *et al.*, *J. Trauma: Injury Inf. Crit. Care* 44:485-491 (1998)).

Probably the most commonly used method for lowering body temperature relies on blankets that circulate water and lower body temperature externally. This method has the advantage of being non-invasive but probably lowers temperature too slowly to be of much benefit to patients that have undergone stroke or traumatic injury.

A second method involves performing cardiopulmonary bypass (CPB) in which a patient's blood is recirculated through a cooling device. This method is capable of

decreasing body temperature relatively rapidly but requires trained medical personnel and is generally impractical outside of a hospital-type setting.

Recently, attempts have been made to reduce body temperature using a patient's respiratory system for heat exchange and, in some cases, devices have been designed for this purpose (see *e.g.*, US 6,303,156; US 2003/0131844; and WO 03/059425). One approach is to simply have a patient inhale physiologically acceptable gases that have been cooled to a low temperature (U.S. 6,303,156). Other approaches have involved administering mists of liquid particles to increase the rate at which heat is exchanged (WO 03/059425; U.S. 2003/0131844; Forman, *et al.*, *J. Surg. Res.* 40:36-42 (1986)). If the liquid present in mists has a boiling point lower than body temperature, *i.e.*, lower than about 37°C, then droplets should be converted into a gas in a patient's respiratory tract and this should be accompanied by an exchange of heat. However, one problem with this procedure is that the conversion of liquid to gas is accompanied by a large expansion of volume and this creates the possibility of alveolar overdistention. Furthermore, the converted gas mixes with the oxygen in the lungs of the patient and this may result in hypoxia and/or hypocarbia.

Summary of the Invention

The present invention is directed to a procedure in which the body temperature of a patient is lowered by administering a mist containing frozen particles. Heat exchange occurs when these particles are converted into a liquid in a patient's respiratory tract. The frozen particles must be small enough so that the droplets that are formed can be easily exhaled. Also, it is important that, after melting, the particles are not converted into a gas which would then dilute the oxygen present in a patient's lungs. Therefore, the liquid from which mists are formed should have a boiling point greater than about 37°C. The invention includes methods for using these mists to treat patients in preparation for surgery or to reduce tissue damage subsequent to stroke, cardiac ischemia or traumatic injury. In addition, the invention includes the mists themselves and systems in which a mist-generating composition is combined with a device capable of generating frozen particles of small diameter.

In its first aspect, the invention is directed to a mist that comprises small diameter frozen particles suspended in a physiologically acceptable carrier gas. The frozen particles must be formed from a non-toxic, physiologically acceptable liquid with a boiling point of greater than 37°C and with a melting temperature of less than 37°C. In order to adequately 5 penetrate deep into a patient's respiratory system, the frozen particles in mists should be no greater than 10 mm in diameter and, preferably, they should be 5 mm or less. The frozen particles should comprise about 0.01-10% (v/v) of mists, preferably 0.05-5% and, more preferably, 0.1-2% (v/v).

10 The most preferred liquid for use in mists is saline, but other fluids such as water may also be used. Physiologically acceptable carrier gases include oxygen, air, sodium hexafluoride, helium and mixtures of these gases. The most preferred of these gases is air, oxygen or a combination of the two. The temperature of the physiologically acceptable gas present in mists should generally be maintained at greater than 0 and less than 37°C. 15 Procedures for lowering the body temperature of patients using low temperature gases have been described in U.S. 6,303,156, and appropriate devices that can be readily adapted for the generation of mists containing small-diameter frozen particles are known in the art (see e.g., U.S. 5,035,750 and WO 03/059425, both of whose teachings are incorporated herein by reference).

20 In another aspect, the invention is directed to a method of rapidly lowering the body temperature of a patient by administering the mists described above for a period of time sufficient to achieve the desired temperature change. This procedure may be performed prior to surgery, especially cardiac or neurosurgery, or it may be performed to reduce tissue 25 damage subsequent to stroke, ischemia or traumatic injury.

The invention is also directed to a system that can be used for lowering the body temperature of a patient by generating the mists described above. The system includes a device capable of generating mists containing frozen particles of 10 mm diameter or less. 30 Any device with this capability may be used, including those referred to above. The system also includes a container having a composition comprising the physiologically acceptable gas and physiologically acceptable liquid from which mists will be generated. These components of mists should have the characteristics described above and the container in

which they are present may either be part of the mist-generating device or may be a separate component that is attached to the device in a manner that allows mist generation. In general, this means that a passageway must be available leading from the container to a port or nozzle from which the composition can be expelled.

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The device must also include a component for cooling the gas/liquid composition prior to expulsion to a degree sufficient to form the small diameter frozen particles. This may be any type of component, or system known in the art for lowering temperature. For example, cooling may result from the expansion of gas that occurs when it passes from a 10 region of high pressure to low pressure. Thus, the cooling component may simply be the opening through which the gas/liquid composition is passed. As discussed previously, the preferred physiologically acceptable gas for use in compositions is air, oxygen or a mixture of the two and the most preferred fluid is saline. The system should preferably also include a component that allows the generated mists to be easily delivered to a patient for 15 inhalation. For example, mists may be directed through an endotracheal tube inserted in the patient or they may be released into a mask designed to cover a patient's nose and mouth.

Detailed Description of the Invention

The present invention is based upon the development of a procedure for lowering a 20 patient's body temperature which utilizes the exchange of heat that occurs when frozen particles are converted into a liquid. Specifically, patients are administered mists containing small-diameter frozen particles that penetrate deep into their lungs and are converted into liquid by absorbing heat from the patient's lungs. The liquid droplets thus formed are of very small diameter, *e.g.*, less than about 10 mm, allowing them to be easily exhaled by the 25 patient. In order to avoid the dilution of available oxygen that occurs when liquid is converted into gas in a patient's lungs, the fluid from which frozen particles are formed should have a boiling point above the body temperature of the patient, *i.e.*, above about 37°C.

30 The most preferred physiologically acceptable liquid for use in the procedure described above is saline. However, other fluids with appropriate characteristics may also be used. The procedure is compatible with any physiologically acceptable gas, with the most preferred being air, oxygen or a combination of air and oxygen. Concentrations of

fluid should be adjusted so that the density of the particles within mists is roughly about 1% on a volume basis. Ranges may be, for example, 0.01-10% (v/v), 0.05-5% (v/v) and preferably, 0.5-2% (v/v). As a general rule, a density of more than about 10% should be avoided in order to avoid a buildup of fluid in a patient's lungs.

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Any device capable of forming a mist with frozen particles of 10 mm diameter or less may be adapted for use with the present procedure. Examples of suitable devices are described in U.S. 2003/0131844, and U.S. 5,035,750. When a physiologically acceptable gas/liquid composition is provided to such a device and the parameters of the device are 10 adjusted to provide a mist of the type described above, a system is formed that can be used for treating patients. Containers having the gas/liquid composition from which mists are formed may be part of the device itself or may be a separate component that is attached to form the system. The mist of frozen particles may be expelled into an endotracheal tube that can be inserted into a patient or it may simply be released from a port that permits 15 inhalation. Another alternative is that mist may be released into a mask designed to cover a patient's nose and mouth. The use of systems for administering inhaled compositions to patients are well known to those of skill in the art of anesthesiology and the adjustment of devices for accomplishing specific clinical objectives can be readily carried out by one of ordinary skill in the art.

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The degree to which a patient is cooled will be determined by clinical considerations on a case-by-case basis. However, in general, body temperature will be lowered by about 2-7°C. Reducing body temperature will be desirable for patients undergoing cardiac surgery or neurosurgery and will also be useful for decreasing the amount of damage that occurs 25 subsequent to stroke, cardiac ischemia and traumatic injury. When temperature reduction is used to decrease tissue damage, the procedure should be initiated as soon as possible after the event causing damage has occurred. Clinical factors that will need to be weighed will include the nature of the injury sustained and whether the patient is taking medication or has a medical condition that suggests that body temperature should not be rapidly reduced. 30 Consideration of such clinical parameters and the adjustment of various treatments to achieve clinical needs are routine in the art of medicine.

What is Claimed is:

1. A mist for lowering the body temperature of a patient, comprising:
 - a) frozen particles, wherein:
 - i) said frozen particles are formed from a nontoxic, physiologically acceptable substance having a boiling point greater than 37°C;
 - ii) said frozen particles melt at a temperature of less than 37°C;
 - iii) said frozen particles are no larger than 10 mm in diameter; and
 - b) a physiologically acceptable carrier gas in which said frozen particles are suspended.
2. The mist of claim 1, wherein said frozen particles comprise 0.01-10% (v/v) of said mist.
3. The mist of claim 1, wherein said frozen particles comprise 0.05-5% (v/v) of said mist.
4. The mist of claim 2, wherein said frozen particles comprise 0.1-2% (v/v) of said mist.
5. The mist of claim 1, wherein said frozen particles are no more than 5 micrometers in diameter.
6. The mist of claim 1, wherein said frozen particles are formed from saline.
7. The mist of claim 1, wherein said frozen particles are formed from water.
8. The mist of claim 1, wherein said physiologically acceptable carrier gas is oxygen, air, sodium hexafluoride ,helium or a mixture of these gasses.

9. The mist of claim 8, wherein said physiologically acceptable carrier gas is air, oxygen or a mixture of air and oxygen.
10. The mist of claim 1, wherein said physiologically acceptable gas carrier gas is cooled to a temperature of greater than 0 and less than 37°C.
11. A method of rapidly lowering the body temperature of a patient, comprising administering the mist of claim 1 to said patient for a period sufficient to lower said body temperature.
12. The method of claim 11, wherein said mist is administered to said patient as a treatment to prevent tissue damage subsequent to spinal injury, stroke, cardiac ischemia or traumatic injury.
13. The method of claim 11, wherein the body temperature of said patient is lowered in preparation for, or during, surgery.
14. The method of claim 13, wherein said surgery is cardiac surgery or neurosurgery.
15. A system useful in lowering the body temperature of a patient, comprising:
 - a) a device capable of generating mists containing frozen particles of 10 micrometers diameter or less;
 - b) a container containing a composition comprising a physiologically acceptable gas and a physiologically acceptable liquid, wherein said liquid has a boiling point of greater than 37°C and wherein said container is either part of said device or can be attached to said device in a manner that allows access of said composition to a passageway that permits said composition to be expelled from said device in such a manner as to form a mist; and
 - c) a cooling component of said device which lowers the temperature of said physiologically acceptable liquid when it is expelled from said device to a degree sufficient that said liquid forms ice particles of 10 micrometers or less.

16. The system of claim 15, wherein said cooling component of said device is a port or nozzle that said composition passes through when it is expelled from said device.
17. The system of claim 15, wherein said physiologically acceptable gas is air, oxygen or a mixture of air and oxygen.
18. The system of claim 15, wherein said physiologically acceptable liquid is water or saline.
19. The system of claim 15, wherein, upon expulsion from said device, a mist is formed having frozen particles of 5 micrometers diameter or less.
20. The system of claim 15, wherein said passageway in said device leads from said container to a mask designed to cover a patient's nose and mouth and into which said mist is expelled.